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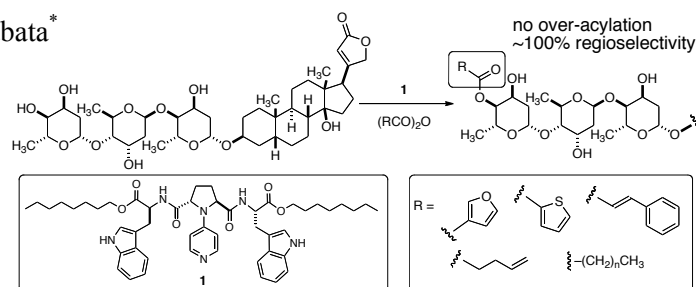
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Graphical Abstract

Perfectly regioselective acylation of a cardiac glycoside, digitoxin, via catalytic amplification of the intrinsic reactivity

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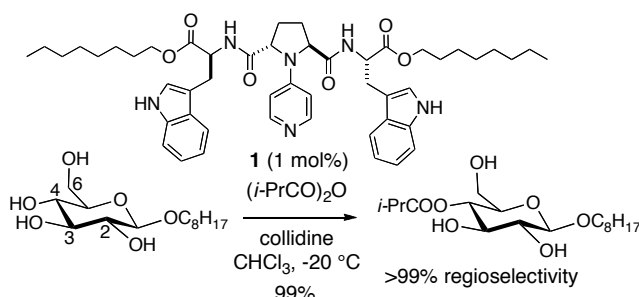
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Abstract—Organocatalytic regioselective acylation of digitoxin has been developed. This method provides the 4''-*O*-monoacylate as the sole product without the concomitant formation of diacylates. The extremely high regioselectivity was assumed to be the result from the combined effects of the high intrinsic reactivity of C(4'')-OH and catalyst-promoted regioselective acylation of the same hydroxy group. © 2010 Elsevier Science. All rights reserved

Chemical modification of bioactive compounds provides ample opportunity to find and develop further potent bioactive derivatives. Functionalization of natural products and pharmaceuticals is one of the most promising approaches to construct valuable library of bioactive molecules.¹ Since bioactive molecules often possess multiple functional groups, their regioselective manipulation without protection–deprotection sequences is an attractive access to the structurally defined and diverse library in minimum steps.² In contrast to the well-developed enzymatic process, nonenzymatic regioselective manipulation of the multifunctionalized molecules such as polyols has been a fundamental challenge in organic synthesis.^{3,4} We have developed an organocatalytic one-step procedure for the chemo- and regioselective acylation

of a secondary hydroxy group of monosaccharides.⁵ With organocatalyst **1**, acylation of the intrinsically less reactive secondary hydroxy group at C(4) of octyl β-D-glucopyranoside proceeded in up to >99 % selectivity in the presence of a more reactive primary hydroxy group at C(6) and two other secondary hydroxy groups at C(2) and C(3) (Scheme 1). Thus, catalyst **1** could control the regioselectivity of the reaction independently from the intrinsic reactivity of the substrate. Indeed, the corresponding acylation with isobutyric anhydride catalysed by 4-dimethylaminopyridine (DMAP) proceeded in a random manner to give four monoacylates (47%, 6-*O*- : 4-*O*- : 3-*O*- : 2-*O*-acylate = 36 : 26 : 26 : 12), diacylates (22%), and recovery of substrate (31%).^{5a,b} In the course of our continuous efforts for regioselective acylation of polyols, we found that the catalyst **1** promoted the perfectly regioselective acylation of digitoxin (**2**) possessing four secondary hydroxy groups (Table 1). The observed high regioselectivity was assumed to be the result from the combined effects of high intrinsic reactivity of the particular hydroxy group and catalyst-promoted regioselective acylation of the same hydroxy group.

We have been interested in regioselective acylation of carbohydrates because it would provide opportunities to develop compounds with potent biological activity.⁶ Digitoxin (**2**) is a well known clinically used cardiac glycoside, which is composed of a digitoxose trisaccharide and an aglycon (digitoxigenin).⁷ Regioselectivity of

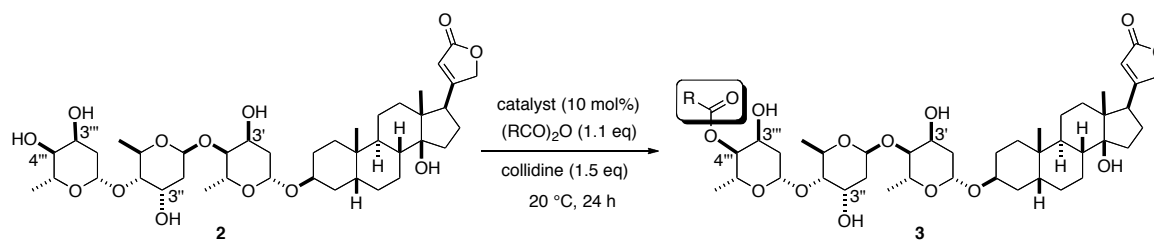


Scheme 1. Regioselective acylation of a glucose derivative.

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Table 1

Selectivity profile of acylation of digitoxin^a



Entry	Catalyst	Acid anhydride (R)	Solvent	Monoacylate (%)	regioselectivity ^b 4'''-O : 3'''-O : 3''-O : 3'-O	Diacylate ^c (%)	Recovery (%)
1	none	Me	CHCl ₃	~0	-	~0	~100
2	DMAP	Me	CHCl ₃	66	>99 : 0 : 0 : 0	18	24
3 ^d	DMAP	Me	CHCl ₃	66	>99 : 0 : 0 : 0	11	20
4 ^e	DMAP	<i>i</i> -Pr	CHCl ₃	80	>99 : 0 : 0 : 0	10	8
5	1	Me	CHCl ₃	98	>99 : 0 : 0 : 0	~0	~0
6 ^f	1	Me	CHCl ₃	92	>99 : 0 : 0 : 0	~0	6
7	1	Me	THF	57	>99 : 0 : 0 : 0	24	15
8	1	Me	DMF	68	>99 : 0 : 0 : 0	15	16
9 ^g	1	Me	pyridine	62	>99 : 0 : 0 : 0	19	14
10 ^e	1	<i>i</i> -Pr	CHCl ₃	98	>99 : 0 : 0 : 0	~0	1
11	1	Ph	CHCl ₃	90	>99 : 0 : 0 : 0	~0	9

^a Reactions were carried out with a substrate concentration of 0.02 M.

^b % Regioselectivity among four monoacylates.

^c 3'''-,4'''-Diacylate.

^d 0.90 equiv. of acetic anhydride was used.

^e Run at -20 °C.

^f 1 Mol% of **1** was used.

^g Run in the absence of collidine.

acylation of **2** was investigated with catalyst **1** and DMAP for the control experiment (Table 1). The 4'''-acetate was obtained as a sole monoacylate in 66% yield together with 18% yield of the 3'''-,4'''-diacetate by treatment of **2** with acetic anhydride in the presence of 10 mol% of DMAP in CHCl₃ at 20 °C for 24 h, while no acylation took place in the absence of DMAP (entries 1 and 2). Similarly, DMAP-catalyzed isobutyrylation of **2** at -20 °C gave the 4'''-isobutyrate as a sole monoacylate in 80% yield, together with 10% yield of the diacylate (entry 4). Over-acylation could not be avoided even by use of less amount of acid anhydride. Treatment of **2** with 0.9 equivalent of acetic anhydride in the presence of 10 mol% of DMAP at 20 °C for 24 h gave 66% yield of monoacylate and 11% of diacylate, together with 20 % recovery of **2**. (Entry 3) The observation indicates that C(4''')-OH is the most reactive among four secondary hydroxy groups of **2**, and C(3''')-OH is the second most reactive.⁸ On the other hand, acetylation of **2** in the presence of 10 mol% of catalyst **1**

gave the 4'''-acetate as a sole product in 98% yield without the concomitant formation of the diacylate (entry 5).⁹ With 1 mol% of **1** the 4'''-acetate was obtained in 92% yield without formation of the diacetate from over-acylation (Entry 6). The 4'''-isobutyrate was also obtained as the sole product in 98% yield from acylation of **2** with isobutyric anhydride in the presence of **1** (Entry 10). Benzoylation took place exclusively at C(4''')-OH without the formation of the diacylate (Entry 11). All of these results indicate that catalyst **1** further accelerates the acylation of C(4''')-OH that has high intrinsic reactivity toward acylation. By the reactions in THF, DMF, and pyridine, diacylates were formed in 15~24% yield even in the presence of catalyst **1** (entries 7-9). The observed solvent effects indicate that hydrogen bonding interaction between the catalyst and the substrate would be responsible for the exclusive formation of the 4'''-O-acylates. In our previous study on catalytic regioselective acylation of carbohydrates, we found that regioselectivity of the acylation depended strongly on the

solvent polarity, and the highest regioselectivity was obtained from the reaction in chloroform. It has been proposed that hydrogen bonding interaction between the catalyst and the substrate would be critically involved for achieving high regioselectivity.^{5a-c}

The predominant formation of the 4'''-acylate catalyzed by DMAP seems to be a reasonable consequence from the high intrinsic reactivity of C(4'''-OH, since the highest reactivity of C(4'''-OH of digitoxin toward acetylation has already been known.⁸ On the other hand, exclusive formation of the 4'''-acylate without over-acylation was achievable only in the presence of catalyst **1**.¹⁰ We assume that acylation of C(4'''-OH would proceed in an accelerative manner in the presence of catalyst **1** as proposed for our previous study on the regioselective acylation of carbohydrates.¹¹ A hypothetical model of transition-state assembly for the regioselective acylation of C(4'''-OH of **2** is shown Figure 1. In the case where hydrogen bond between axial C(3'''-OH¹² and an amide carbonyl of the acyl pyridinium ion is formed, the substrate would adopt a conformation in which equatorial C(4'''-OH is in the close proximity to the reactive carbonyl group of the acyl pyridinium ion, resulting in the selective acylation of C(4'''-OH. The observed solvent effects on the ratio of mono-/diacylation (entries 5-9) are consistent with the expected strength of the hydrogen bonding interactions depending on the solvent polarity. However, this seems merely a tentative understanding for the exclusive formation of 4'''-O-acylate, on the assumption that the amide carbonyl group preferentially form a hydrogen bond with axial C(3'''-OH rather than equatorial C(4'''-OH.¹³ On the other hand, the hydrogen bonding effect may also decelerate the second acylation of the 4'''-O-acylate to give the diacylate. Actually, treatment of **3** (R=Ac) under the identical conditions to those for Entry 5 of Table 1 (**1** in CHCl₃), in which the significant hydrogen bonding is expected, gave 99% recovery of **3**, while that for Entry 7 (**1** in THF) or Entry 2 (DMAP in CHCl₃), in which less significant or no hydrogen bonding effect is expected, gave the diacylate 20% (80% recovery) or 24% yield (76% recovery), respectively. These results also suggest that the 3'''-4'''-diacetate was formed via acylation of the 4'''-acylate. We finally examined whether selective formation of the 4'''-O-acylate could be the result from the migration of the 3'''-O-acylate. Treatment of the 3'''-acetate¹⁴ of digitoxin under the conditions identical to those for Entry 5 in Table 1 except for the absence of acetic anhydride gave quantitative recovery of the 3'''-acetate without any trace of formation of the 4'''-acetate. This clearly indicates that the exclusive formation of the 4'''-O-acylates is the result from the kinetic control by catalyst **1**.

Introduction of various acyl groups into C(4'''-OH of **2** was examined (Table 2). Regioselective lipidation of **2** was achieved with anhydrides derived from long-chain saturated fatty acids such as lauric (dodecanoic), palmitic (hexadecanoic), and behenic (docosanoic) acid, giving the corresponding 4'''-O-monoacylate as the sole product in 92%, 90%, and 96% yield, respectively, in the presence of **1** (entries 1–3). An acyl group derived from an unsaturated

fatty acid was introduced exclusively at C(4'''-OH (entry 4). Heteroaromatic carbonyl groups such as thiophene carbonyl and furan carbonyl groups were also introduced at C(4'''-OH exclusively in 94% and 93% yield, respectively (entries 5 and 6). Similarly, a cinnamoyl group was introduced at C(4'''-OH exclusively in 90% yield (entry 7). While 2–8% recovery of **2** was observed, the formation of the diacylate was negligible in the each run of acylation of **2** promoted by **1**.

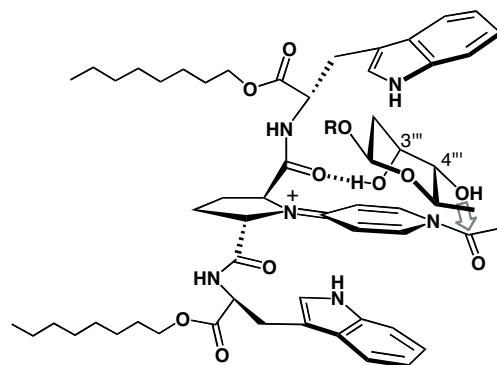


Figure 1. A hypothetical model of transition-state assembly for regioselective acylation of digitoxin (**2**) (the terminal digitoxose is shown) promoted by catalyst **1**.

Table 2

Regioselective acylation of **2** with various acid anhydride^a

<div> <div> <div>2</div> <div> <div>1 (10 mol%)</div> <div>(RCO)₂O (1.1 eq)</div> </div> <div>→</div> <div>3</div> </div> <div> <div>collidine (1.5 eq)</div> <div>CHCl₃, 20 °C, 24 h</div> </div> </div>							
Entry	R	regioselectivity ^b				Yield ^c	Recovery
		4'''-O	: 3'''-O	: 3'''-O	: 3'-O	(%)	(%)
1	C ₁₁ H ₂₃	>99	: 0	: 0	: 0	92	7
2	C ₁₅ H ₃₁	>99	: 0	: 0	: 0	90	8
3	C ₂₁ H ₄₃	>99	: 0	: 0	: 0	96	2
4	CH ₂ =CH-(CH ₂) ₂	>99	: 0	: 0	: 0	90	7
5	2-thiophene	>99	: 0	: 0	: 0	94	4
6	3-furyl	>99	: 0	: 0	: 0	93	5
7	(E)-Ph-CH=CH	>99	: 0	: 0	: 0	90	6

^a Reactions were carried out with a substrate concentration of 0.02 M.

^b % Regioselectivity among four monoacylates.

^c Formation of 3'''-O-, 4'''-O-diacylate was negligible in each run.

In summary, we have developed a method for organocatalytic regioselective acylation of digitoxin. This method provides the 4'''-*O*-monoacylate as the sole product without the concomitant formation of diacylates. The extremely high regioselectivity was assumed to be the result from the combined effects of the high intrinsic reactivity of C(4''')-OH of digitoxin and catalyst-promoted regioselective acylation.

Acknowledgments

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Supplementary data

Supplementary data associate with this article can be found, in the online version, at doi: /j.tetlet.

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9. *Typical procedure of regioselective acylation of digitoxin* (Table 1, entry 3): Digitoxin (30 mg, 0.039 mmol), catalyst **1*** (3.3 mg, 3.9 μ mol, 10 mol %) and 2,4,6-collidine (7.7 μ L, 0.059 mmol, 1.5 equiv.) were dissolved in CHCl₃ (2.0 mL). After stirring for 10 min at 20 °C, acetic anhydride (4.1 μ L, 0.043 mmol, 1.1 equiv) was added to the mixture. The mixture was stirred for 24 h at 20 °C. The reaction was quenched with 1N aq. HCl and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by SiO₂ column chromatography (ethyl acetate/hexane = 3 : 1) to give pure 4'''-*O*-acetyl digitoxin (31 mg, 98%). M.p. 219–223 °C. [α]_D +19 (c 0.1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 5.87 (s, 1H), 4.99 (d, *J* = 17.4 Hz, 1H), 4.95–4.85 (m, 3H), 4.80 (d, *J* = 17.4 Hz, 1H), 4.60 (dd, *J* = 9.8, 2.5 Hz, 1H), 4.24–4.22 (m, 3H), 4.10–3.90 (m, 2H), 3.90–3.70 (m, 2H), 3.24 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.22 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.06 (s, 1H), 2.91 (s, 1H), 2.78 (bt, 1H), 2.20–1.30 (m, 29H), 2.12 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 174.6, 169.7, 117.6, 98.3, 98.1, 95.3, 85.6, 82.5, 82.3, 77.2, 74.5, 73.4, 72.5, 68.2, 68.0, 67.2, 66.4, 66.2, 50.9, 49.6, 41.8, 40.0, 37.4, 37.1, 36.6, 36.2, 35.7, 35.1, 33.1, 30.1, 29.7, 26.8, 26.6, 26.5, 23.6, 21.4, 21.1, 21.09, 21.00, 18.1, 17.9, 15.7. IR (KBr) 3484, 2935, 1780, 1742, 1622, 1450, 1405 cm⁻¹. MS *m/z* (FAB) *m/z* (rel intensity) 829 (MNa⁺, 10), 252 (35). HRMS (FAB) Calcd for C₄₃H₆₆O₁₄Na: 829.4350, Found: 829.4347. Analysis of the product was further performed with H–H COSY, HMQC, HMBC (see Supplementary data).
10. Catalyst **1** is commercially available from Wako Pure Chemical Industries, Ltd.
11. In the regioselective acylation of octyl β -D-glucopyranoside by catalyst **1**, it was found that the higher ratio of the C(4)-*O*-acylation was associated with the higher ratio of mono-/diacylation, indicating that the acylation at C(4)-OH would proceed in an accelerative manner, see: references 5a and 5b.
12. The conformation of digitoxose and digitoxin in solution has been studied in detail, see: (a) Coxon, B. *J. Carbohydr. Chem.* **1984**, *3*, 525–543. (b) Drakenberg, T.; Brodelius, P.; McIntyre, D. D.; Vogel, H. J. *Can J. Chem.* **1990**, *68*, 272–277.
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14. The 3''',4'''-*O*-acetate of digitoxin was prepared by hydrolysis of the 3''',4'''-diacetate with K₂CO₃ in MeOH at -20 °C.